Jasmine / Judy

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GENENTECH Oncology and IDEC Pharmaceuticals
INVESTIGATOR INITIATED PROTOCOL CONCEPT WORKSHEET

DATE: June 18, 1997

STUDY TITLE: Phase I-II Study of IDEC-C2B8 in CLL

INVESTIGATOR

Name: Susan O'Brien, M.D.
Address 1: UT M.D. Anderson Cancer Center/Leukemia
Address 2: 1515 Holcombe Blvd. Box 061
Address 3: Houston, TX 77030
Phone: 713)792-7305 Fax: 713)794-4297
E-mail: None

SUB-INVESTIGATOR(s): (Yes) or No (If yes, please complete the Addendum)

SCIENTIFIC RATIONALE: CD20 is expressed in 97% of cases of CLL. Although flourescence intensity is less than in lymphoma, the number of binding sites is high at about 61×10^3/cell. As such, CLL should be an excellent target disease for use of this antibody.

STUDY OBJECTIVE(s): See attached

STUDY ENDPOINT(s): See attached

* PK studies should be included.
Would Genentech take serum in PK studies?

TREATMENT DESIGN

Drugs	Units	Route	Cycle Days	Cycle	Duration
C2B8	mg/m^2	IV	1	weekly	4-8 wks

NUMBER OF PATIENTS: Open for Phase I

TIMELINE (Projected MM/YY)

IRB Approval: 3 mos
First Patient Enrolled: 3 mos
Last Patient Enrolled: 9-12 mos

SUPPORT REQUIRED

Drug: (Yes) or No Total mg: _____
* Grant: (Yes) or No $ Amount: _____

* Funding is very limited for trial support.

GENENTECH Oncology and IDEC Pharmaceuticals
INVESTIGATOR INITIATED PROTOCOL CONCEPT WORKSHEET—ADDENDUM

GENENTECH INITIATED PROTOCOL CONCEPT SHEET
ADDENDUM

Sub-Investigator #1 Information	Michael Keating, M.D., D.S.
Name:	UT M.D. Anderson Cancer Center/Leukemia
Address 1:	1515 Holcombe Blvd. Box 92
Address 2:	Houston, TX 77030
Phone:	713) 795-2376
Fax:	713) 794-1807
E-mail:	

Sub-Investigator #2 Information	Hagop Kantarjian, M.D.
Name:	UT M.D. Anderson Cancer Center/Leukemia
Address 1:	1515 Holcombe Blvd. Box 61
Address 2:	Houston, TX 77030
Phone:	713) 792-7305
Fax:	713) 794-4297
E-mail:	

Sub-Investigator #3 Information	Moshe Talpaz, M.D.
Name:	UT M.D. Anderson Cancer Center/Biolmmunotherapy
Address 1:	1515 Holcombe Blvd. Box 302
Address 2:	Houston, TX 77030
Phone:	713) 792-3522
Fax:	713) 796-2173
E-mail:	

Name of first Genentech/IDEC Contact: _____

Next Steps: _____

Mail Completed Form To:

Genentech, Inc. *Jasmine Martin, RN, MSN, FNP,CS*
Medical Science Liaison

10867 Snowy Cloud Trail, Littleton, CO 80125
(303) 973-5768 FAX: (303) 973-1924
PAGER: (800) 946-4646 PIN: 1413951 E-MAIL: jmartin@gene.com

GENENTECH Oncology and IDEC Pharmaceuticals
Investigator Initiated Protocol Concept Worksheet - addendum

June 18, 1997

Phase I-II Study of IDEC-C2B8 in CLL

Studies in lymphoma have shown a lower response rate in WDLL (the tissue equivalent of CLL) as well as lower serum levels of the antibody. Serum levels are also lower in patients with bulky disease. In CLL there is a significant amount of disease in the blood that may act as a "sink" for absorption of the antibody. Consequently it is possible that higher doses and/or longer exposure may be useful in CLL. Since there is no MTD yet at doses up to 500 mg/m^2 we would propose further escalation in Phase I fashion. However to limit duration of therapy on Day 1 (when infusions are prolonged secondary to acute toxicity with the first dose) the first dose would be 375 mg/m^2 (about 6 hour infusion) but all subsequent doses would be higher (but the same); perhaps starting with 500 mg/m^2 and escalating by 33%.

The first endpoint would be MTD (or stopping early if high doses were given with significant activity. The other endpoint would be efficacy which could be assessed on the Phase I portion (since we know we are starting with effective doses in lymphoma) and then on the Phase II.

Patients would be treated for 4 weeks and reevaluated. Patients in CR would not receive further therapy but those with stable disease, minor responses, or partial responses would complete 4 more weeks of therapy.

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OBrien
final

THE UNIVERSITY OF TEXAS M. D. ANDERSON CANCER CENTER

DIVISION OF MEDICINE

Phase I/II Study of IDEC-C2B8 (Rituximab) for Relapsed CLL

STUDY PRINCIPAL INVESTIGATOR:

Susan O'Brien, M.D.

STUDY CO-PRINCIPAL INVESTIGATOR:

Michael J. Keating, M.B., B.S.

STUDY COLLABORATORS:

Miloslav Beran, M.D., PhD, D.V.M.

Francis Giles, M.D.

Jorge Cortes, M.D.

Hagop Kantarjian, M.D.

Elihu Estey, M.D.

Charles Koller, M.D.

Emil Freireich, M.D.

From the Leukemia Service, Division of Medicine, The University of Texas
M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, Texas 77030.

Michael Andreeff, M.D., PhD

Steven Kornblau, M.D.

From the Molecular Hematology and Therapy Service, Division of Medicine,
The University of Texas M.D. Anderson Cancer Center,
1515 Holcombe Blvd., Houston, Texas 77030

Introduction and General Plan

This is a Phase I/II study of IDEC-C2B8 (Rituximab) for relapsed CLL.

IDEC-C2B8 is a chimeric IgG 1 kappa monoclonal antibody with mouse variable and human constant regions that recognizes the CD20 antigen expressed on normal B cells and most malignant B cell lymphomas. Several human studies have already been completed with this antibody. All of them have been done in lymphoma patients. A Phase I study with a single dose schedule used a highest dose of 500 mg/m^2 without dose limiting toxicity. Acute side effects included fever, chills, headache, nausea, rash, none of which were severe. A Phase I schedule using a weekly times 4 infusion was performed in patients with relapsed B cell lymphoma. Dose levels were 125, 250, and 375 mg/m^2. Twenty patients were entered in the dose finding study; there was no dose limiting toxicity and the maximum tolerated dose was not attained. Side effects were related mainly to the first infusion and were fever, chills, rash, headache, etc., typical antibody type reactions. Subsequent infusions were associated with markedly less toxicity and the incidence of severe toxicity was <5%. Clinical activity was documented in 11 of 18 evaluable patients and 375 mg/m^2 was chosen for the Phase II portion of the study.

Recently results from the pivotal Phase III study were presented. One hundred sixty-six patients with advanced stage low grade or follicular lymphoma were enrolled. Side effects were usually mild to moderate and were associated with the first infusion. There were 80 responders for a response rate of 48%.

These studies showed a much lower response rate in WDLL (the tissue equivalent of CLL) as well as lower serum levels of the antibody. Serum levels are also lower in patients with bulky disease. In CLL there is a significant amount of disease in the blood that may act as a "sink" for absorption of the antibody. Consequently, it is possible that higher doses and/or longer exposure would be useful in CLL. Since there is no MTD yet at doses up to 500 mg/m^2, we are proposing further escalation in a Phase I fashion.

However, to limit duration of therapy on day one (when infusions are prolonged secondary to acute toxicity with the first dose) the first dose in all patients would be 375 mg/m^2 (about a six hour infusion) but all subsequent doses would be higher (but the same); starting with 500 mg/m^2 and escalating to 650, 825, and 1 gm/m^2. Once an MTD is reached, patients will be entered on the Phase II portion of the protocol to further define efficacy.

PROTOCOL ABSTRACT

PROTOCOL:

PHASE I/II STUDY OF IDEC-2B8 (RITUXIMAB) FOR RELAPSED CLL

STUDY CHAIRPERSON:

Susan O'Brien, M.D.

OBJECTIVES:

To evaluate the safety and efficacy of IDEC-C2B8 (Rituximab) in patients with CLL.

RATIONALE:

IDEC-C2B8 is a chimeric IgG1 kappa monoclonal antibody, with mouse variable and human constant regions, that recognized the CD20 antigen expressed on normal B cells and most malignant B-cell lymphomas. IDEC-C2B8 shows specificity for the CD20 antigen and binds with an apparent affinity of 5.2×10^{-9}M. Thirty-four evaluable patients with advanced stage low-grade lymphoma were enrolled in a Phase II study at a dose level of 375 mg/m^2 once weekly for four weeks. There were 16 responders (3 CRs and 13 PRs). The B-cell antigen CD20 is expressed in 97% of cases of CLL. As such, CLL should be an excellent target disease for the use of the IDEC antibody.

Studies in lymphoma have shown a lower response rate in WDLL (the tissue equivalent of CLL) as well as lower serum levels of the antibody. Serum levels are also lower in patients with bulky disease. In CLL there is a significant amount of disease in the blood that may act as a "sink" for absorption of the antibody. Consequently it is possible that higher doses and/or longer exposure may be useful in CLL.

PATIENT ELIGIBILITY:

Diagnosis of previously treated CLL Rai III-IV or earlier stage disease with evidence of "active disease" as defined by the NCI-sponsored working group 1) weight loss of >10% in prior 6 months, 2) extreme fatigue, 3) fever or night sweats without evidence of infection, 4) worsening anemia or thrombocytopenia, 5) progressive lymphocytosis with a rapid lymphocyte doubling time, 6) marked hypogammaglobulinemia or paraproteinemia, or 7) lymphadenopathy ≥5 cm.

- Age 15 years or above.
- Adequate renal or hepatic functions (creatinine ≤2 mg%, bilirubin ≤2 mg%). Patients with renal or liver dysfunction due to organ infiltration by lymphocytes are eligible.
- Performance status ≤3 (Zubrod scale Appendix A).
- Signed informed consent.

TREATMENT PLAN:

1. The first dose of Rituximab will be 375mg/m^2. All patients will receive the same first dose.
2. Subsequent doses will be fixed for any given patient and will be administered weekly for 3 weeks.
3. At least 3 patients will be studied at each dose level and evaluated for 7 days before starting additional patients on escalated doses.
4. Starting dose: 350 mg/m^2 for the first dose and 500 mg/m^2 for 3 subsequent doses.
5. Subsequent escalations will be at 33% increments.

See Section 5.0 for complete details.

STATISTICAL CONSIDERATION:

For Phase I: The major objective of the Phase I portion of the study is to determine the maximum tolerated dose. Further objectives are to evaluate the efficacy and toxicity associated with the drug. At lease three patients will be entered at each dose level. It is estimated that the accrual rate will be approximately 30 patients. The estimated accrual time is about 12 months.
For Phase II: A two-stage design as proposed by Simon, will be used to decide between: H_1:p ≤.20, a response rate of no real interest and H_2:p ≥.40, a response rate of considerable interest. The design is in two stages, 17 patients in the first stage and 20 patients in the second stage. If the response rate is ≤17.6% (3/17) or less, the study may be terminated at the end of the first stage. If the response rate is ≤27% (10/37) at the end of the second stage, then this therapy would not be recommended for further study. this design has an average sample size of 26 patients (assuming a true response rate of 20%) and a probability of early termination of 55% (assuming a true response rate of 20%). the type 1 and 2 error rates are 10%.

PRETREATMENT AND TREATMENT EVALUATION:

Pretreatment
CBC, plts, differential, SMA 12, Bone marrow aspirate, biopsy, β_2M, Tumor measurements, radiologic studies as indicated, Quantitative immunoglobulins (IgG, IgA, IgM), Peripheral blood lymphocyte markers: CD4, CD8, CD14, CD16, CD19, CD20, CD5, CD19 and simultaneous CD5 + CD19

Follow-up Studies:
CBC, plts, differential every 7 days, Bone marrow aspirate, biopsy at end of therapy and then every 6 months, β_2M at end of therapy, Tumor measurements, appropriate radiologic studies at the end of therapy and then every 6 months, Quantitative immunoglobulins at the end of therapy, Peripheral blood lymphocyte markers: CD4, CD8, CD14, CD16, CD19, CD20, CD5, CD19 and simultaneous CD5 + CD19 at the end of therapy.

ESTIMATED ACCRUAL:

IT IS ESTIMATED THAT ACCRUAL WILL BE 3 PARTICIPANTS PER MONTH.

SITE OF STUDY: (PLEASE CIRCLE THE APPROPRIATE ANSWER)

INPATIENT	OUTPATIENT	BOTH

LENGTH OF STAY: (WHAT IS LENGTH & FREQUENCY OF HOSPITALIZATION?)

Not required.

RETURN VISITS: (HOW OFTEN MUST PARTICIPANTS COME TO MDACC?)

Weekly for 4 weeks then q 3 months.

HOME CARE: (SPECIFY WHAT, IF ANY, TREATMENT MAY BE GIVEN AT HOME)

None.

WHERE WILL STUDY BE CONDUCTED:

A) ONLY AT MDACC	B) MDACC + COMMUNITY PROGRAMS (CCOP, NETWORK)	C) INDEPENDENT MULTI-CENTER ARRANGEMENTS

NAME OF SPONSOR/FUNDING SOURCE:

Genentech, Incorporated.

COMPETING PROTOCOLS: (PROTOCOL NUMBERS)

DM97-036

NAME OF RESEARCH NURSE/DATA MANAGER RESPONSIBLE FOR PROTOCOL:

Susan Lerner

1.0 OBJECTIVES

To evaluate the safety and efficacy of IDEC-C2B8 (Rituximab) in patients with CLL.

2.0 BACKGROUND

Current CLL Therapy

CLL has a variable prognosis depending on its presentation, stage and extent of prior therapy (1). Most patients with CLL progress into advanced stages, become treatment refractory, and die from complications of marrow failure (infections, bleeding) and from progressive disease. About 10-20% of patients have disease evolution into Richter's syndrome (RS) (large cell: 10%, prolymphocytic {PLL}10%) or rarely an acute lymphocytic leukemia (ALL)-like picture. Nucleoside-based therapy with fludarabine or chlorodeoxyadenosine has become the mainstay of CLL therapy (2). Fludarabine is superior to alkylating agents (e.g., chlorambucil) or combination therapy (CAP, CHOP) in terms of inducing CR, overall remission rates, and remission durations (1). Patients with CLL who become fludarabine refractory have a very poor prognosis. The response rate to any further regimen except transplant is 20% or less, and the median survival is less than 12 months (3).

3.0 BACKGROUND DRUG INFORMATION

3.1 Preclinical Experience

IDEC-C2B8 (IDEC-102) is a chimeric IgG1 kappa monoclonal antibody, with mouse variable and human constant regions, that recognizes the CD20 antigen expressed on normal B cells and most malignant B-cell lymphomas (4). This antigen, important in cell cycle initiation and differentiation, is expressed strongly in over 90% of B-cell lymphomas. IDEC-C2B8 shows specificity for the CD20 antigen and binds with an apparent affinity of 5.2×10^{-9}M. *In vitro* mechanism of action studies have demonstrated that this antibody binds human complement and lyses lymphoid B cell lines. It has significant activity in assays for antibody-dependent cellular cytotoxicity (ADCC). High dose safety studies in cynomolgus monkeys have revealed no adverse clinical events. There were no significant abnormalities on laboratory tests or on histopathology. As predicted, the biologic effect of IDEC-C2B8 is manifested by B-cell depletion in peripheral blood (PB), lymph nodes (LN) and bone marrow (BM). Three weeks after 4 weekly doses there was a >75% decrease of B cells in the bone marrow. Recovery of the B cells in the peripheral blood (to >75% of baseline) usually occurred within 60 days following the last dose.

3.2 Clinical Experience

A Phase I clinical trial in patients with non-Hodgkin's lymphoma (NHL) was conducted at Stanford University Medical Center (5). Fifteen (15) heavily pretreated patients (3 per dose level) with low-grade relapsed B-cell lymphoma received single doses (10, 50, 100, 250, or 500 mg/m^2) of IDEC-C2B8 given intravenously. Treatment-related symptoms "were mild to moderate." They consisted of fever (5 patients), skin rash (4 patients), nausea (2 patients), rigor (2 patients), orthostatic hypotension (2 patients) and bronchospasm (1 patient). No significant toxicities were observed during 3 months of post treatment follow up. Serum C3, IgG, IgA, and IgM levels; platelets, neutrophils and T-cell counts were unchanged. Pharmacokinetics of free antibody at the three higher dose levels revealed a serum half-life of 4.4 days (range 1.6 - 10.5). Serum levels of IDEC-C2B8 over 10 μg/mL (range 13.5 - 105) persisted in 6 of 9 patients over 14 days. CD20-positive B cells were rapidly depleted in the peripheral blood at 24-72 hours and remained depleted for 2-3 months in most patients. Two-week post infusion tumor biopsies showed IDEC-C2B8 antibody bound to tumor cells and a decrease in the percentage of B cells. Tumor responses occurred in 6 of 9 patients (2 partial and 4 minor responses).

Based on these encouraging results to a single dose of chimeric anti-CD20 antibody, a multiple dose study in patients with relapsed B-cell lymphoma was initiated (6). Treatment consisted of weekly x 4 infusions of IDEC-C2B8. Dose levels of 125, 250, and 375 mg/m^2 were explored. Using this dosing schedule it was anticipated that antibody accumulation would occur in some patients and that they would experience prolonged exposure (sustained blood levels) to IDEC-C2B8 throughout the therapeutic course. Saturation of the tumor sites was also expected for those patients in whom IDEC-C2B8 accumulation occurred. Twenty patients were entered in the Phase I dose-finding portion of the study: 10 males and 10 females, median age 60, mostly low grade lymphoma, 17/20 stage III/IV at diagnosis, with a median of 2 prior chemotherapy regimens. There was no dose-limiting toxicity and the maximum tolerated dose was not attained. The hypothesis of IDEC-C2B8 accumulation and prolonged antibody exposure was confirmed. Infusional symptoms were brief, manageable, and primarily associated with the first infusion. Pharmacokinetic analysis revealed a $t_{1/2}$ of 1.9 days and 7.8 days following the first and fourth infusions, respectively. Circulating B cells were rapidly depleted. There were no clinically significant changes in median serum immunoglobulin levels. No quantifiable anti-C2B8 antibody reactivity (HAMA or HACA) was observed. Complement levels decreased in some patients without correlation to response. Clinical activity was documented in 11 of 18 evaluable patients. There were seven (7) partial and four (4) minor responses. These occurred primarily in patients with low-grade lymphoma (7 partial and 3 minor responses in 13 patients).

One hundred sixty-six (166) patients with advanced stage low-grade or follicular lymphoma were enrolled in the pivotal Phase III portion of the study (7-10). IDEC-C2B8 was administered at a dose level of 375 mg/m^2 once weekly for four weeks. There were 105 males and 61 females with a median age of 58 years (range, 22-79) and 40% of patients were over 60 years of age. All patients had relapsed with a median of 3 (range, 1-7) prior chemotherapy regimens. Of the 166 patients, 161 completed all four infusions. Side effects (chills, fever, nausea, vomiting, headaches) were usually mild to moderate and associated with the first IDEC-C2B8 infusion. The mean half-life of free (serum) antibody was 1.8 days following the first dose and 6.2 days following the fourth infusion. Quantifiable immunoreactivity (HAMA or HACA) was not observed. There were 80 responders (10 CRs and 70 PRs); a response rate of 48% (95% CI: 41-56%). The median time to onset of response was 50 days (range 21-288 days). Thirty-eight (38) of the responses are ongoing. The median duration of response has not been reached after 9.2 months (range 1.9 to 18.8+ months). The response rate in 23 patients previously treated with ABMT was 78% compared with a 43% response rate in patients who had not undergone ABMT.

3.3 IDEC-C2B8 in CLL

The B-cell antigen CD20 is expressed in 97% of cases of CLL. Although fluorescence intensity is somewhat less than in low grade lymphoma, the number of binding sites is high, calculated at about 61 x 10^3 per cell. As such, CLL should be an excellent target disease for the use of the IDEC antibody.

Studies in lymphoma have shown a lower response rate in WDLL (the tissue equivalent of CLL) as well as lower serum levels of the antibody. Serum levels are also lower in patients with bulky disease. In CLL there is a significant amount of disease in the blood that may act as a "sink" for absorption of the antibody. Consequently it is possible that higher doses and/or longer exposure may be useful in CLL. Since there is no MTD yet at doses up to 500 mg/m^2 we would propose further escalation in Phase I fashion. However, to limit duration of therapy on Day 1 (when infusions are prolonged secondary to acute toxicity with the first dose) the first dose would be 375 mg/m^2 (about 6 hour infusion) but all subsequent doses would be higher (but the same); starting with 500 mg/m^2 and escalating by 33%. Once an MTD is reached, patients will be entered on the Phase II portion of the protocol to further define efficacy.

3.4 Origin of the IDEC-C2B8 Cell Line

The chimeric mouse/human anti-CD20 monoclonal antibody, IDEC-C2B8 (IDEC-102), is a human gamma 1 kappa antibody with mouse variable regions isolated from

a murine anti-CD20 monoclonal antibody (2B8). This chimeric antibody, which is secreted by the Chinese hamster ovary (CHO) transfectoma clone 8-8F12-5E5-50C9, binds with high affinity to CD20-positive cells, performs human effector functions in *in vitro* assays, and specifically depletes B cells *in vivo*. The CHO transfectoma was produced by inserting DNA coding for the chimeric immunoglobulin chains into the CHO cell line DG44 by electroporation, and selecting for a clone resistant to G418 (Geneticin) that secreted chimeric immunoglobulin (Clone 8-8F12). Subsequently, the immunoglobulin production was enhanced through selection of a clone resistant to 5 nM methotrexate (MTX) (clone 8-8F12-5E5); Phase I and Phase II material was produced using this clone. Immunoglobulin production was further enhanced through selection of a clone resistant to 50nM MTX (clone 8-8F12-5E5-50C9). Material produced from this clone has been used in a Phase II combination study with CHOP.

3.5 Storage/Preparations

3.51 Investigational Drug Nomenclature

- IDEC Pharmaceuticals code designation IDEC-C2B8 (IDEC-102)
- Generic Name: rituximab
- IND Number: BB-IND 4904

3.52 Clinical Formulation

Clinical supplies for this study will be manufactured by either IDEC Pharmaceuticals in San Diego, CA or Genentech Incorporated in South San Francisco, CA.

Rituximab from either source will be provided to the clinical sites packaged in single use 10 mL (100mg) and 50 mL (500mg) Type I glass vials at a concentration of 10 mg of protein per mL. The product is formulated in 7.35 mg/mL sodium citrate buffer, containing 7 mg/mL polysorbate 80, 9.0 mg/mL sodium chloride and Sterile Water for Injection. The pH is adjusted to 6.5.

Rituximab may be produced by the mammalian (Chinese Hamster Ovary) cell suspension culture in a nutrient medium containing 100 mg/mL of the antibiotic gentamicin. The antibiotic is not detectable in the final product.

3.53 Storage

Rituximab for clinical use should be stored in a secure refrigerator at 2-8°C.

3.54 Reconstitution and Dilution of IDEC-C2B8

Using a sterile syringe and a 21 gauge or larger needle, transfer the necessary amount of Rituximab from the vial into a partially filled IV pack containing sterile, pyrogen-free 0.9% Sodium Chloride, USP (saline solution). The final concentration of Rituximab should be 1mg/mL. Mix by inverting the bag gently.

Caution should be taken during the preparation of the drug (see Appendix I). Parenteral drug products should be inspected visually for particulate matter prior to administration. Preparations of Rituximab containing visible particles should not be used. As with all parenteral drug products, aseptic procedures should be used during the preparation and administration of Rituximab.

NOTE: DO NOT USE A VACUUM APPARATUS to transfer IDEC-C2B8 from the syringe to the infusion pack. DO NOT USE evacuated glass containers which require vented administration sets, because this causes foaming when air bubbles pass through the solution.

4.0 ELIGIBILITY CRITERIA

4.1 Diagnosis of previously treated CLL Rai III-IV or earlier stage disease with evidence of "active disease" as defined by the NCI-sponsored working group 1) weight loss of >10% in prior 6 months, 2) extreme fatigue, 3) fever or night sweats without evidence of infection, 4) worsening anemia or thrombocytopenia, 5) progressive lymphocytosis with a rapid lymphocyte doubling time, 6) marked hypogammaglobulinemia or paraproteinemia, or 7) lymphadenopathy ≥5 cm.

4.2 Age 15 years or above.

4.3 Adequate renal or hepatic functions (creatinine ≤2 mg%, bilirubin ≤2 mg%). Patients with renal or liver dysfunction due to organ infiltration by lymphocytes are eligible.

4.4 Performance status ≤3 (Zubrod scale Appendix A).

4.5 Signed informed consent.

5.0 TREATMENT PLAN

CAUTION: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.

5.1 Premedication (two tablets [375mg or 500mg] of acetaminophen orally and 25 to 100 mg diphenhydramine hydrochloride orally or intravenously) will be administered 30 to 60 minutes prior to starting each infusion of Rituximab. **Patients will not be administered dexamethasone or other glucocorticoids.**

5.2 The drug may be administered via a peripheral or central intravenous line.

5.3 During the Rituximab infusion, the patient's vital signs (blood pressure, pulse, respiration, temperature) should be monitored every 15 minutes x 4 or until stable and then hourly until the infusion is discontinued. Available at the bedside prior to Rituximab administration will be epinephrine for subcutaneous injection, diphenhydramine hydrochloride for intravenous injection, and resuscitation equipment for emergency management of anaphylactoid reactions.

5.4 The initial dose rate at the time of the first IDEC-C2B8 infusion should be 50 mg/hr for the first half hour. If no toxicity is seen, the dose rate may be escalated gradually **(50 mg/hour increments at 30-minute intervals)** to a maximum of 300 mg/hr. If the first dose of Rituximab is well tolerated, the starting flow rate for the administration of doses 2-4 will be 100 mg/hour then increased gradually **(100 mg/hour increments at 30-minute intervals)** not to exceed 400 mg/hr.

5.5 Patients may experience transient fever and rigors with infusion of chimeric anti-CD20 (IDEC-C2B8) antibody. When these side effects are noted, the antibody infusion should be slowed or interrupted, the patient should be observed and the severity of the side effects should be evaluated. The patient should be treated according to the best available local practices and procedures. Following observation, when the patient's symptoms improve, the infusion should be continued, initially, at ½ the previous rate (see table below). Upon resolution of all side effects and in the judgment of the investigator, the patient's dose may be gradually escalated (50 mg/hr increments at 30-minute intervals) to a maximum rate of 300 mg/hr. Following the antibody infusion, the IV line should be kept open for medications, as needed. If complications occur during the Rituximab infusion, the patient should be observed for two hours after the completion of the infusion.

Dose Rate	Fever	or	Rigors	or	Mucosal Congestion/ Edema	or	% Drop in Systolic BP
Decrease to ½	> 38.5°C		Mild/Moderate		Mild/Moderate		> 30 mm Hg

5.6 Since transient hypotension has been reported during Rituximab infusions, consideration should be given to withholding anti-hypertensive medications the day of the Rituximab infusion.

5.7 First Dose

The first dose of Rituximab will be 375 mg/m^2. All patients will receive the same first dose.

5.8 Subsequent doses will be fixed for any given patient and will be administered weekly for 3 weeks.

5.9 Escalation Schedule

5.91 At least 3 patients will be studied at each dose level and evaluated for 7 days after the first dose before starting additional patients on escalated doses.

5.92 All treatment will be given at M.D. Anderson Cancer Center. Patients will receive their infusions either as inpatients or in the Ambulatory Treatment Center.

5.93 Dose Schedule: Patients will receive 4 weekly doses of Rituximab. The first dose for all patients is 375 mg/m^2. Subsequent weekly doses (x 3) will be the same in a given patient, but escalated in a Phase I fashion (see below).

5.94 Dose escalation in the study will follow the schema below:

Starting Dose: 375 mg/m^2 for the first dose and 500 mg/m^2 for 3 subsequent doses.

Dose Level	1st dose (mg/m^2)	Subsequent doses (mg/m^2)
0	375	500
1	375	650
2	375	825
3	375	1000

5.95 The MTD definition will be as follows:

a. Three patients are studied at the first dose level.

b. If none experience dose limiting toxicity, then the next higher dose is used for the subsequent group of 3 patients.

c. If 2 or more experience dose limiting toxicity at a dose level, then the MTD has been exceeded and 3 more patients are treated at the next lower dose (if only 3 patients were treated previously at this dose).

d. If 1/3 experience dose limiting toxicity at the current dose, then 3 more patients are accrued at the same dose. If 0 of these three experience dose limiting toxicity, then the dose is escalated. Otherwise the MTD has been exceeded and 3 more patients are treated at the next lower dose.

5.96 Once a maximum tolerated dose is defined, the Phase II portion of the study will commence. Thirty patients will be entered.

5.97 A minimum of 1 course (4 weekly infusions) will be required for a patient to be considered as having received an adequate trial to evaluate efficacy. All patients will be considered evaluable for toxicity.

6.0 PRETREATMENT AND FOLLOW-UP STUDIES (See Appendix B):

6.1 Pretreatment (within 2 weeks of the start of therapy)

- CBC, plts, differential
- SMA 12
- Bone marrow aspirate, biopsy
- β_2M
- Tumor measurements, radiologic studies as indicated
- Quantitative immunoglobulins (IgG, IgA, IgM)
- Peripheral blood lymphocyte markers: CD4, CD8, CD14, CD16, CD19, CD20, CD5, CD19 and simultaneous CD5 + CD19

6.2 Follow-up Studies:

- CBC, plts, differential every 7 days
- Bone marrow aspirate, biopsy at end of therapy (within one month of the last

dose) and then every 6 months
- β_2M at end of therapy
- Tumor measurements, appropriate radiologic studies at the end of therapy and then every 6 months
- Quantitative immunoglobulins at the end of therapy
- Peripheral blood lymphocyte markers: CD4, CD8, CD14, CD16, CD19, CD20, CD5, CD19 and simultaneous CD5 + CD19 at the end of therapy.

7.0 RESPONSE CRITERIA

SITE	CR	PR
Nodes	None	≥50% decrease
Liver/Spleen	Not palpable	≥50% decrease
Symptoms	None	N/A
PMN	>1,500/μl	>1,500/μl or >50% improvement from baseline
Platelets	>100,000/μl	>100,000/μl or >50% improvement from baseline
Hemoglobin (untransfused)	>11.0 g/dl	>11.0 g/dl or >50% improvement from baseline
Lymphocytes	>4,000/μl	>50% decrease
Bone Marrow aspirate	<30% lymphocytes	N/A for PR
Biopsy	No lymphocyte infiltrate	< 30% lymphocytes with residual disease on biopsy for nodular PR

8.0 REMOVAL FROM STUDY

8.1 Progressive or Relapsed Disease.

Progressive disease (PD) will be characterized by at least one of the following:

a. ≥50% increase in the sum of the products of at least two lymph nodes on two consecutive examinations two weeks apart (at least one node must be ≥2 cm). Appearance of new palpable lymph nodes.

b. ≥50% increase in the size of liver and/or spleen as determined by measurement below the respective costal margin; appearance of palpable hepatomegaly or splenomegaly which was not previously present.

c. ≥50% increase in absolute number of circulating lymphocytes and at least 10,000/μl.

8.2 Patient request.

9.0 STATISTICAL CONSIDERATIONS

9.1 Phase I

The major objective of the Phase I portion of the study is to determine the maximum tolerated dose. Further objectives are to evaluate the efficacy and toxicity associated with the drug. At least three patients will be entered at each dose level. It is estimated that the accrual rate will be approximately 30 patients. The estimated accrual time is about 12 months.

9.2 In patients refractory to fludarabine there is no regimen which produces a response rate of > 20-30%.

In previously treated patients not refractory to fludarabine, the response rate to fludarabine and cyclophosphamide (DM95-049) is ~80% with almost all responses being PR. In addition, this regimen is associated with significant myelosuppression (AGC < 1000 in 77% of patients) and infections (severe infection 25%, neutropenic fever 30%, minor infection 25%).

Rituximab has not been associated with myelosuppression (AGC < 1000 in 2.5%) or infections. Given the lack of toxicity (except for first-dose reactions) so far seen with this drug, a response rate lower than that seen with the fludarabine and cyclophosphamide regimen would still be acceptable. Thus, a response rate of ≥40% would be of further interest.

9.3 A two-stage design as proposed by Simon, will be used to decide between:

H_1:p ≤.20, a response rate of no real interest

H_2:p ≥.40, a response rate of considerable interest

The design is in two stages, 17 patients in the first stage and 20 patients in the second stage. If the response rate is ≤17.6% (3/17) or less, the study may be terminated at the end of the first stage. If the response rate is ≤27% (10/37) at the end of the second stage, then this therapy would not be recommended for further study. this design has an average sample size of 26 patients (assuming a true response rate of 20%) and a probability of early termination of 55% (assuming a true response rate of 20%). the type 1 and 2 error rates are 10%.

10. REFERENCES

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6. Maloney et al, Proc ASCO 1994:13:304
7. Grillo-López et al, Soc Bio Therapy (Abstract) 1994
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1. Investigational Brochure, IDEC Pharmaceuticals, July 1997

APPENDIX A

PERFORMANCE STATUS

GRADE	SCALE
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Ambulatory, capable of light or sedentary work. Restricted in physically strenuous activity.
2	Ambulatory, capable of all self-card, but not of work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

APPENDIX B

STUDY FLOW CHART

Study Procedures	Pretreatment[5]	Each Infusion	Weekly	End of Therapy[6]	Every 6 Months
Informed Consent	X				
Physical Examination	X		X	X	X
Chest X-ray/CT scan	X[1]			X[1]	X[1]
Vital Signs	X[2]	X[2]			
Hematology	X		X	X	X
Lymphocyte Markers[3]	X			X	X
Bone Marrow Biopsy/Aspirate	X			X	X
Rai/Binet Staging	X			X	X
Lymph Node Assessment	X			X	X
Immunoglobulin Assay[4]	X			X	X

[1] If clinically indicated
[2] Every 15 minutes x 4 and then hourly until end of infusion
[3] CD3, CD4, CD8, CD14, CD16, CD19, CD20, CD5, CD19, simultaneous CD5 + CD19
[4] IgA, IgG, IgM
[5] Within 2 weeks of the start of therapy
[6] Within one month after the last dose

APPENDIX C

GUIDELINES FOR REPORTING OF ADVERSE DRUG REACTIONS (ADRs) FOR MDACC CLINICAL RESEARCH STUDIES TO THE SURVEILLANCE COMMITTEE

In general, ADRs are defined as:

1) PREVIOUSLY UNKNOWN TOXICITIES (not included in the list of known toxicities provided by the Division of Cancer Treatment (DCT); and
2) LIFE-THREATENING OR FATAL TOXICITIES (regardless of whether or not previously unknown.

The timely reporting of adverse drug reactions is required by the Food and Drug Administration (FDA). The reporting of adverse reactions is in addition to and does not supplant the reporting of toxicities as part of the report of the results of the clinical trial. The Surveillance Committee (IRB) must be notified of any significant life-threatening and/or serious adverse reactions or experiences regardless of cause on a timely basis and must be apprised of all adverse experiences by written report on a periodic and timely basis, at least annually.

1. Reporting ADRs occurring with Investigational Agents

Phase I Studies

Life-threatening events (Grade 4) which may be due to drug administration	Submit a written report within 10 working days to the Surveillance Committee
All fatal events (Grade 5) while on study (or within 30 days of treatment)	
First occurrence of any previously unknown clinical event (Regardless of Grade)	

Phase II and III Studies - Unknown Reactions

Grades 2-3	Submit a written report within 10 working days to the Surveillance Committee
Grades 4 and 5	

Phase II and III Studies - Known Reactions	
Grades 1-3	No report is required, except as part of study results
Grades 4 and 5	Submit a written report within 10 working days to the Surveillance Committee Exceptions: - Grade 4 myelosuppression need only be submitted as part of the study results.

2. Reporting ADRs Occurring with Commercial Drugs

Any increased incidence of a known ADR as reported in the package insert and/or the literature, any ADR which is both serious (life-threatening, fatal) and unexpected or any death on study if clearly related to commercial agent.	Submit a written report to the Surveillance Committee within 10 working days.

3. Devices in Clinical Research

Grade 4 and 5 toxicities	Submit a written report to the Surveillance Committee within 10 working days.

NOTE: Report event by telephone within 24 hours to study sponsor or FDA (if study is conducted under an institutional IND).

MD ANDERSON
CANCER CENTER

MEMORANDUM

DATE: January 17, 1997

TO: Moshe Talpaz, M.D.
Chairman
Department of Boimmunotherapy

FROM: Susan O'Brien, M.D.
Associate Professor of Medicine
Department of Hematology

SUBJECT: Possible clinical trials at M. D. Anderson using IDEC-C2B8

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1). Refractory or relapsed chronic lymphocytic leukemia.

The B-cell antigen CD20 is expressed in 97% of cases of CLL. Although fluorescence intensity is somewhat less than in low grade lymphoma, the number of binding sites is high, calculated at about 61 x 10^3 per cell. As such, CLL should be an excellent target disease for use of the IDEC antibody

Once patients are refractory to alkylating agents and fludarabine there is no standard of care. Multiple trials have shown that the best response that can be achieved is 10 - 20%, usually with very dose-intensive myelotoxic chemotherapy. This would be an excellent group of patients in which to explore monoclonal antibody therapy and in fact, given the lack of any standard therapy this would also be a reasonable group to provide a NDA for various drugs. As you know, the data using fludarabine in CLL generated by M. D. Anderson was the major data leading to approval of that drug in that disease.

Since fludarabine has become commercially available, the largest cohort of patients that we see at our institution are those that are refractory to both alkylators and fludarabine. On a recent study that was open to previously treated and untreated patients, the percentage of patients who had received fludarabine and alkylators was approximately 70% of patients enrolled on the protocol

Accrual of patients with CLL to protocols is very brisk at M. D. Anderson. The number of referrals per year was flat at about 50 until fludarabine was investigated by Keating and colleagues in the leukemia group at M. D. Anderson (see attached curve). When fludarabine was in clinical trials and the anti-leukemic activity became apparent our accrual increased from 50 to over 200 patients per year. Because we are now regarded as a major center for

innovative research in CLL, there has not been a major drop-off in the referrals as can be seen by the attached curve; we had over 150 new patients referred last year. It's likely that disseminating the information on the availability of a clinical trial using IDEC-C2B8 in CLL will significantly enhance accrual as was seen previously with fludarabine. In addition, this is facilitated nowadays by both our Leukemia Newsletter that is sent to 8,100 physicians, as well as our Web site.

2). Minimal residual disease in CLL.

Fludarabine can produce complete remissions in approximately 50% of patients when used as initial therapy. About another 30% would be in complete remission except for evidence of minimal disease such as nodules on bone marrow biopsy or flow cytometry documenting residual CD5+ B-cells. These patients are ideal targets for using a monoclonal antibody. There is no problem with penetration or exposure of the cells to the antibody because there is no bulky disease and there is free flow between blood and bone marrow. In CLL most minimal residual disease exists in the bone marrow rather than in lymph nodes or spleen.

Our group has previously shown a significant difference in time to progression depending on whether residual disease can be documented by flow cytometry after chemotherapy. Thus, we have an immediate endpoint which can be assessed and quantitated by flow cytometry and a later endpoint which is time to progression. We have significant historical control data for this population with over 700 CLL patients in the data base.

3). Combination with fludarabine in CLL.

There is significant animal data now suggesting that the combination of chemotherapy and monoclonal antibody may be synergistic in lymphoproliferative diseases. Thus, exploring the IDEC antibody along with our most effective single agent chemotherapy would be an attractive concept. In the salvage setting fludarabine alone produces an overall response rate of about 50% with only 20% complete remissions. Thus non-refractory, but relapsed patients, would be an excellent target to try and increase the response seen with single agent fludarabine; this could easily be demonstrated with a relatively small number of patients given the overall response rate of only 50%. Again we have extensive historical data and the response rate has been very well defined both by ourselves and in others.

4). Mantle cell lymphoma/leukemia.

This is a poor prognostic disease with the worst features of both low grade and high grade lymphoma. Currently we do have a regimen that's active in these patients, hyper CVAD, producing responses in up to 90%. However, 50% of those responses are partial. Thus. further consolidation with the IDEC antibody would be very attractive in these patients who

have residual disease but would still not have bulky disease at the time of treatment. This is not a common disease but because of widespread publicity about our hyper CVAD protocol we have been able to accrue 45 patients in just 20 months on that study.

5). Philadelphia chromosome + ALL.

This disease has an excellent initial response to chemotherapy with complete remission rates of about 80%. However, essentially 100% of patients will relapse. Different approaches have been tried for remission maintenance in this disease including interferon (based on the efficacy of that drug in Philadelphia chromosome + CML) as well as autologous transplant. Allogeneic transplant has cured some patients but most patients are not eligible because of age and lack of donor. This is a disease that is considered uniformly fatal with standard therapy and would be an excellent target disease in which to use the IDEC-C2B8 since these patients can be rendered into remission but the problem is maintaining that remission. This is also a fertile area for an active drug to be used for a NDA.